

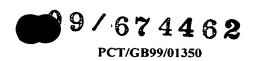
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21 RGVASFVCEY ••I•••••	81 KVNLTIQGLR Q	141 SSGLFFYSFL	SEQ ID:1 (pCTLA4) Human CTLA4 Cattle CTLA4
11 AQPAVVLANS •••••S• T.•P•••S•	71 STCTGTSTEN • I • • • • SG •	131 DFLLWILAAV •••••••	PIN SEQ II ••• Human ••• Cattle
I PVFSKGMHV •••C•A••	61 VEDELTFLDD MGN•••••	121 VIDPEPCPDS	181 CEKQFQPYFI
-10 PCTALFSLLF •••L•F••	51 V••••••M V••••G••M	111 VGMGNGTQIY L•I•••A••	171 YVKMPPTEPE
-30 -20 MACSGFRSHG AWLELTSRTW •••L••QR•K •Q•N•AA•••	GSAGKAAEVR VTVLRRAGSQ A•P••T•••••Q•D•• E•S••D•••	101 VELLYPPPYY •••MYPPPYY	161 KKRSPLTTGV
-30 MACSGFRSHG •••L••QR•K	31 GSAGKAAEVR A•P••T•• E•S••D•••	91 AVDTGLYICK VEL <u>LY</u> •M••••••• <u>MY</u>	151 ITAVSLSKML L

51



ATGGCTTGCT CIGGATICCG	GAGCCATGGG • C• G•• CAA•	GCTTGGCTGG •••CA•••A A••••	AGCTTACTTC • C • GG • G • G •	TAGGACCTGG
CCCTGTACAG CTCTGTTTTCCCTGTACAG CTCTGTTTTC	B1 TCTTCTCTTC	91 ATCCCTGTCT	101 TCTCCAAAGG •••G••••C	111 GATGCACGTG AA.T
131 CAGTAGTGCT • T • G • A • • • 6 • • • • 6 • • • • • • • • •	141 GGCCAACAGC ••••G•••	151 CGGGGTGTTG ••A••CA•C•	161 CCAGCTTTGT	171 GTGTGAGTAT ****************************
191 GCAAAGCTGC •••••CA•	201 CGAGGTCCGG T	211 GTGACAGTGC	221 TGCGGCGGGC •T•••A••	231 CGGCAGCCAG T•A•••••
251 TCTGTGCCGC	261 GACATATACT ACC.TG	271 GTGGAGGATG AG.A	281 AGTTGACCTT	291 CCTTGATGAC •••A••••T
311 CTGGCACCTC •G•••••	321 CACCGAAAAC ••GT•G•••T	AAAGTGAACC		351 AGGCTGAGA
	T	T	T	Tremertory Garceringer Gerindering Accitating Tremertory Congences Gerindering Accitating Tremertory Congences Gerindering Accitating Tremertory Tremertory Accitating 151 Cagtagerery Geroacage Cegegerery Ceagerery Tregones Tremertory Geroacage Cegegery S 131 251 Cagtagerery Geroacage Gegegery Geroacage Cagtagerery Geroacage Gegegery Tregones Cagagerery Geroacage S 201 Cagtagerery Georga Geroacage Tregones Cagagerery Geroacage Tregones Cagagerery Geroacage Tregones Cagagerery Geroacage Tregones Cagagerery Geroacage Tregones Geroacagaaacage Tregones Geroacagaacage Tregones Geroacagaacagaacage Tregones Geroacagaacage Tregones Geroacagaacagaacage Tregones Geroacagaacagaacagaacagaacagaacagaacagaaca



361 GCCGTGGACA •••A•••••	371 CTGGGCTCTA G.G.A	381 CATCTGCAAG ••••••• TG•••••	391 GTGGAGCTCC	401 TGTACCCACC	411 ACCCTACTAT G. A C
421 GTGGGTATGG CC.A.	431 GCAACGGGAC •••••AG•	441 CCAGATTTAT 	451 GTCATTGATC	461 CAGAACCATG	471 CCCAGATTCT
481 GATTTCCTGC ••••••C•	491 TCTGGATCCT	501 GGCAGCAGTT T	S11 AGTTCAGGGT	521 TGTTTTTTA	S31 CAGCTTCCTC TT
541 ATCACAGCTG C	551 TTTCTTTGAG	561 CAAAATGCTA	571 Aagaaaagaa	581 GTCCTCTTAC •C•••••	S91 TACAGGGGTC A
601 TATGTGAAAA	611 TGCCCCGAC	621 AGAGCCAGAA	631 TGTGAAAAGC	641 AATTTCAGCC	651 TTATTTTATT
661 CCCATCAATT	671 GA ••	SEQ ID: 2 (p Human CTLA4 Cattle CTLA4	(pctla4) A4 LA4		

FIG. 3 (CONTD.)

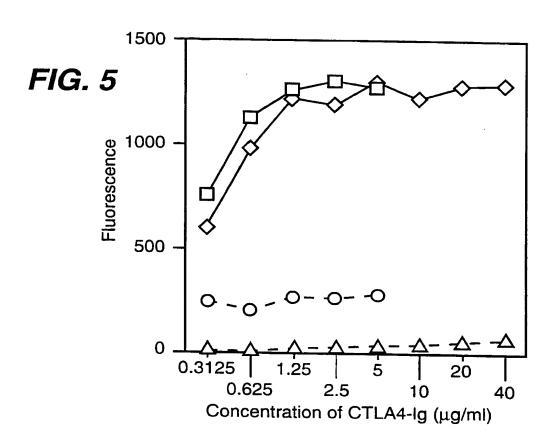
21	81	141	201	261
RGVASFVCEY	KVNLTIQGLR	KSCDKTHTCP	YVDGVEVHNA	KAKGQPREPQ
-30 -20 -10 1 11 21	31 41 51 61 71	111 121 131 141	191	
MACSGFRSHG AWLELTSRTW PCTALFSLLF IPVFSKGMHV AQPAVVLANS RGVASFVCEY	GSAGKAAEVR VTVLRRAGSQ MTEVCAATYT VEDELTFLDD STCTGTSTEN	VGMGNGTQIY VIDPEPCPDS D <u>GGSGGAA</u> EP KSCDKTHTCP	HEDPEVKFNW	
1	61	121	151 161 171 181 191	221 231 241 251
I PVFSKGMHV	VEDELTFLDD	VIDPEPCPDS	PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS
-10	51	111	171	231
PCTALFSLLF	MTEVCAATYT	VGMGNGTQIY	KDTLMISRTP	VLHQDWLNGK
-20		91	161	221
AWLELTSRTW	VTVLRRAGSQ	AVDTGLYICK VELLYPPPYY	PSVFLFPPKP	STYRVVSVLT
-30	31	91	151	211
MACSGFRSHG	GSAGKAAEVR	AVDTGLYICK	PCPAPELLGG	KTKPREEQYN

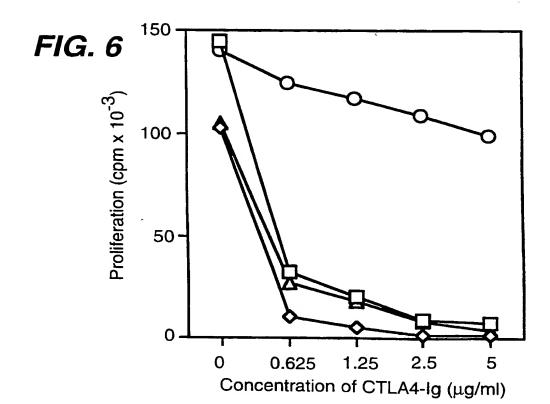
331 341 351 361 SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK

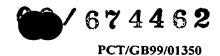
301 311 321 AVEWESNGQP ENNYKTTPPV LDSDGSFFLY

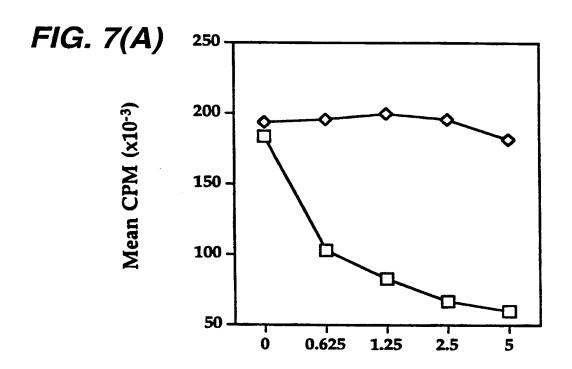
271 281 291 VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI



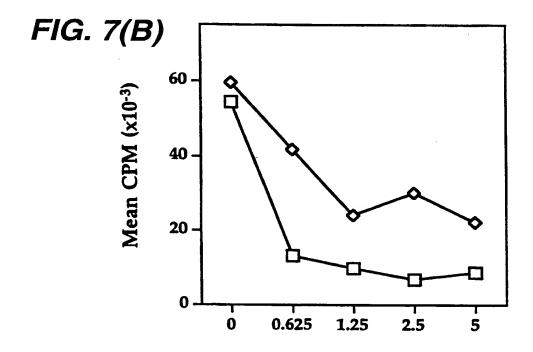






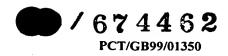


Concentration of CTLA4-Ig (µg/ml)



Concentration of CTLA4-Ig (µg/ml)





71agccrcrgga	151	231a	311	391	471	551	631 GGCTCCGGTC	711
sl	141		301	381TGGCGGTA	461r	541r	621	701 711 GACCAAGCTG ACCGTCCTAG
51r	101 111 121 131	181 191 201 211 221	291 GCAAGAGCTG	371c	451	531cccaaactcc	611	691r
21 31 41	121crccagggaa	201cogracca	281	361	441	511 521	591 601 611	661 671 681 691
31	111	191c	271	351as	431	511	591	671argeargac
			261agagccgagg	341c	421	501	581cc	661
1 11	81 91	171	251	321 331	401 411 grcrgcrgc Acreacecac	491r	571	651
1c	81 TTCACCTTTA	161 171 ragrager agcacara	241	321 331 TGGGGCCAAG GTACCCTG	401 411 grcrerecc	481 491 ACATCGGAAG TAATTATG1	561 571	641 651

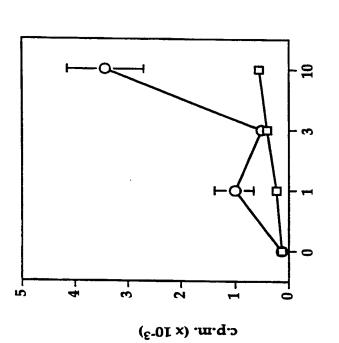
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71s	151TISCSGSSSN
61 ADSVKGRFTI	141sasgrpggrv
1 11 21 31 41 51 61 71 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA ISGSGGSTYY ADSVKGRFTI SRDNSKNTLY	81 91 101 111 121 131 141 151 LOMNSLRAED TAVYYCARAG RILFDYWGOG TLVTVSSGGG GSGGGGGGGG ALOSVLTOPP SASGTPGORV TISCSGSSSN LINKER
41 PGKGLEWVSA	121 GSGGGGSGS
31s	1111 TLVTVSSGGG G
21s	101 RILFDYWGQG
1 11 EVQLVESGGG LVQPGGSLRL	31 91
1 EVQLVESGGG	81 LQMNSLRAED

161...... 171...... 181...... 191...... 201...... 211...... 221...... 231...... IGSNYVYWYQ QLPGTAPKLI IYRNNQRPSG VPDRFSGSKS GTSASLAISG LRSEDEADYY CAAWDDSLVF GGGTKLTVLG



Stimulators (x10 -4)

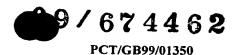
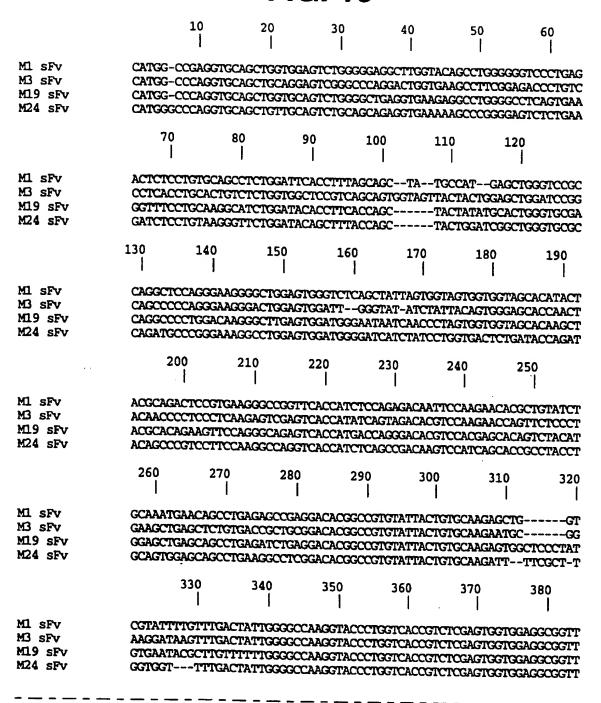


FIG. 10



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	390 	400	410 	420	430 	440 	
Ml sFv	CAGGCGGAGG	TECTETEC	GGTAGTGCA	بلمانات لاماناني	GTGCTGACTC	C 001000	
M3 sFv	CAGGCGGAGG	TEGETETEGE	GGTAGTGCA	CTTCACTCT	GTGCTGACTC2	GCCACCC	TCAGC
M19 sFv	CAGGCGGAGG	TEGETETEGE	GTAGTGCA	THE CHICK	GAGCTGACTCA	GCACCC	CONCE
M24 sFv	CAGGCGGAGG	TEECTCTEEC	GGTAGTGCA	TTGACATO	CAGTTGACCCA	CILATORICA I	OCTOI
						orcreenie.	11001
	450 4	60 <i>4</i>	170	480	490	500	510
	1	1		1	1	Ī	i
Ml sFv	CTCTCCCACC	~~~~~			•	•	'
M3 sFv	GICIGGALC	CCCGGGCAGA	GGGTCACCA'	CICITGIT	CTGGAAGCAGC	TCCAACATCG	GAAGT
M19 sFv	GICLICAGACC	TTCCCACACA	GGGTCACCA	CICITGIA	CTGGAAGCAGC	TCCAACATCG	GAAGT
M24 sFv	GTCTGCATCT	TIGGGYCYGY	CAGICAGGA,	I CACATGCC	AAGGAGACAGC	CTCA	GAAGC
	orcroanci	O T WOOM ON CH	WAGTCACCA:	CACTIGCC	GGCCAGI	CAGGGCATT-	AGC
	520	530	540	550			
	i	1	340	550	560	570	
	•	1		1	j	1	
M1 sFv	AATTATGTAT	ACTGGTACCA	GCAGCTYCC	CCDDCCC	~~~~		
M3 sFv	AATTATGTAT	ACTGGTACCA	GCAGCTCCC	700074CGC/	CCCHAMCICC	TCATCTATAG	SAATA
M19 sFv	TATTATGCAA	GCTGGTACCA	GCAGAAGCC	AGGACAGGC	CCCTGTACTTC	TCATCTATAG	AI'AA£
M24 sFv	AGTTATTTAG	CCTGGTATCA	GCAAAAACC	AGGGAAAGC	CCCTAAGCTYC	TCATCIA1GG	よなななな
						·1001CIAIGC	IGCAI
	580	590	600	610	620	630	640
	i		l		1	Ī	Ī
Ml sFv	ልጥንርጥን	Caller Section	~~~~	Manana a a		·	•
M3 sFv	ATCAGCGGCC	CICHAGAGAIL	CCTGACCGA:	FICICIGGC	ICCAAGICIGG	CACCICAGCC	TCCCT
M19 sFv	ATCAGCGGCC	CICARRORIT	CCTGACCGA.	TOTOTOGC	ICCAAGICIGG	CACCTCAGCC	TCCCT
M24 sFv	ACAACCGGCC CCACTTTTGCA	y y CLUCOCCUT.	CCAGACCGA;		AGTGGATCTGG	AAACACAGCT	TCCTT
	00.0111001	2201000010	CCATCAAGG	LICAGCGGG	AGIGGATCIGG	GACAGAATTC	ACTCT
	650	660	670) 6	80 69	0 70	^
		Ī		j G		0 70	Ų
•	•	'	•	l	•	J.	ł
M1 sfv	GGCCATCAGT	GGCTCCGGT	CCGAGGATG	GCTGATT	ATTACTICTICA	CCATCCCATC	20200
M3 sFv	GGCCATCAGI	GGCTCCGGT	CCGAGGATG	AGGCTGATT	ATTACTICTCA	באותביביאותים	20260
M19 sFv	GACCATCACT	GGGCTCAGG	CGGAAGATG	AGGCTGACT	ATTACTOTAAC	TYTYTTCACACA	יווים ערים
M24 sFv	CACAATCAGC	AGCCTGCAGC	CTGAAGATTT	TGCAACTT	ATTACTGTCA-	ACAGCTTA	PUDCU.
							111001
	710	720	730	740	750		
	İ	1	1		Ī		
MI other	arma			-	•		
M1 sFv M3 sFv	CTGG	PATTCGGCGG	AGGGACCAAG	CTGACCGIC	CTAGGTGC		
M19 sFv	CIGI-TIG	PATTUGGCGG	AGGGACCAAC	CTGACCGT	CTAGGTGCGG	CCCC	
M24 sFv	GGTTTTACTG	VATILGGCGG	AGGGACCAAG	CTGACCGT	CTAGGTGC		
LILT DEV	TACCGCTTGAG	JULIUGGCCA	AUGGACCAA(CTGGAAATY	AAACCTC-		

FIG. 10 (CONTD.)

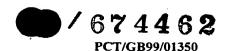
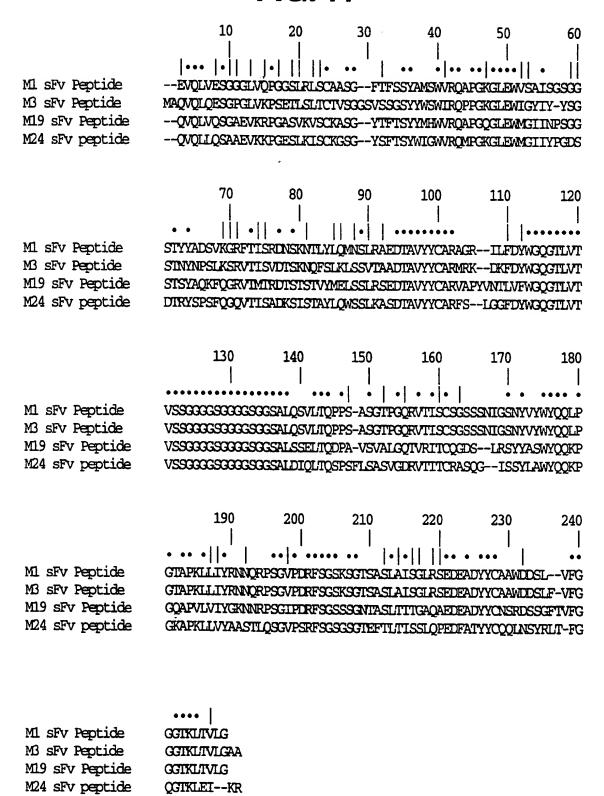


FIG. 11



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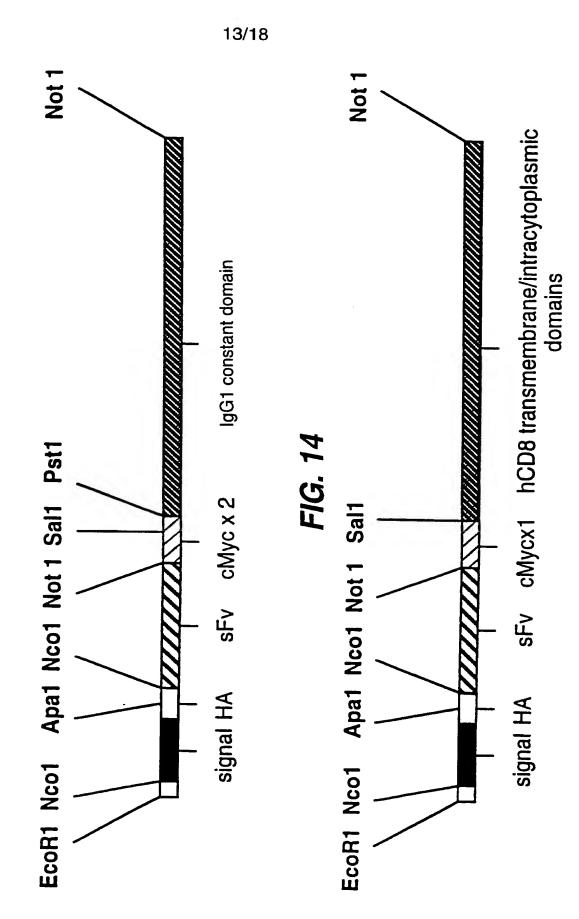




FIG. 15(A)

-65	AGCTTCAGGA	TCCTGAAAGG	TTTTGCTCTA	CTTCCTGAAG	ACCTGAACAC
-15	CGCTCCCATA	AAGCC <u>ATG</u> GC	TTGCCTTGGA	TTTCAGCGGC	ACAAGGCTCA
36	GCTGAACCTG	GCTACCAGGA	CCTGGCCCTG	CACTCTCCTG	TTTTTTCTTC
86	TCTTCATCCC	TGTCTTCTGC	AAAGCAATGC	ACGTGGCCCA	GCCTGCTGTG
136	GTACTGGCCA	GCAGCCGAGG	CATCGCCAGC	TTTGTGTGTG	AGTATGCATC
186	TCCAGGCAAA	GCCACTGAGG	TCCGGGTGAC	AGTGCTTCGG	CAGGCTGACA
236	GCCAGGTGAC	TGAAGTCTGT	GCGGCAACCT	ACATGATGGG	GAATGAGTTG
286	ACCTTCCTAG	ATGATTCCAT	CTGCACGGGC	ACCTCCAGTG	GAAATCAAGT
336	GAACCTCACT	ATCCAAGGAC	TGAGGGCCAT	GGACACGGGA	CTCTACATCT
386	GCAAGGTGGA	GCTCATGTAC	CCACCGCCAT	ACTACCTGGG	CATAGGCAAC
436	GGAACCCAGA	TTTATGTAAT	TGATCCAGAA	CCGTGCCCAG	ATTCTGACTT
486	CCTCCTCTGG	ATCCTTGCAG	CAGTTAGTTC	GGGGTTGTTT	TTTTATAGCT
536	TTCTCCTCAC	AGCTGTTTCT	TTGAGCAAAA	TGCTAAAGAA	AAGAAGCCCT
586	CTTACAACAG	GGGTCTATGT	GAAAATGCCC	CCAACAGAGC	CAGAATGTGA
636	AAAGCAATTT	CAGCCTTATT	TTATTCCCAT	CAATTGAGAA	TT

FIG. 15(B)

MACLGFORHK AQLNLATRTW PCTLLFFLLF IPVFCKAMHV AQPAVVLASS RGIASFVCEY

31 41 51 61 71 81
ASPGKATEVR VTVLRQADSQ VTEVCAATYM MGNELTFLDD SICTGTSSGN QVNLTIQGLR

91 101 111 121 131 141
AMDTGLYICK VELMYPPPYY LGIGNGTQIY VIDPEPCPDS DFLLWILAAV SSGLFFYSFL

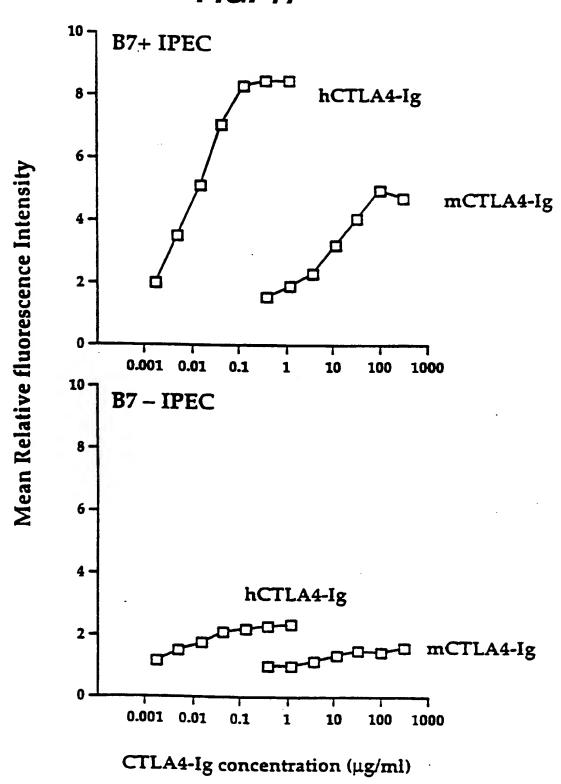
151 161 171 181 LTAVSLSKML KKRSPLTTGV YVKMPPTEPE CEKQFQPYFI PIN

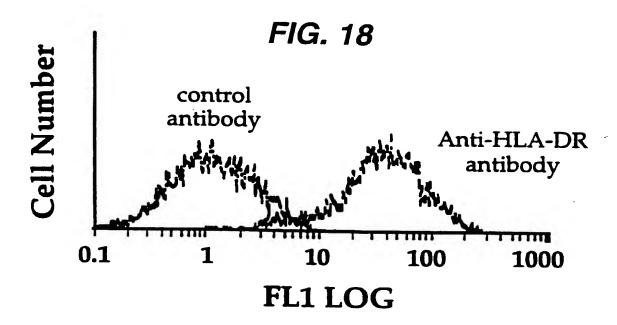


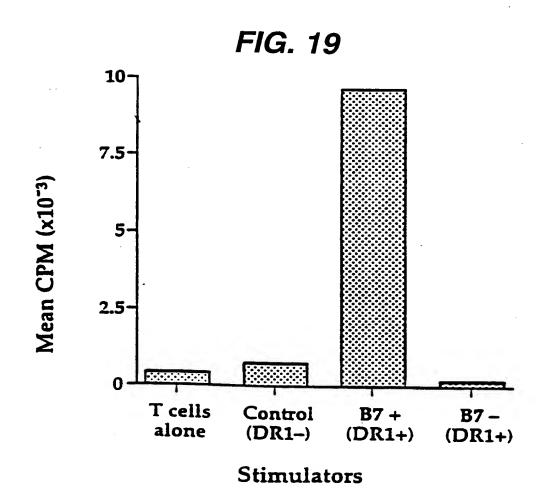
FIG. 16

-36	AAGCTTCGAG	CCAAGCAGCG	TCCTGGGGAG	CGCGTC <u>ATG</u> G	CCTTACCAGT
L5	GACCGCCTTG	CTCCTGCCGC	TGGCCTTGCT	GCTCCACGCC	GCCAGGCCGA
55	GCCAGTTCCG	GGTGTCGCCG	CTGGATCGGA	CCTGGAACCT	GGGCGAGACA
L15	GTGGAGCTGA	AGTGCCAGGT	GCTGCTGTCC	AACCCGACGT	CGGGCTGCTC
L65	GTGGCTCTTC	CAGCCGCGCG	GCGCCGCCGC	CAGTCCCACC	TTCCTCCTAT
215	ACCTCTCCCA	AAACAATCCC	AAGGCGGCCA	AGGGGCTGGA	CACCCAGCGG
265	TTCTCGGGCA	AGAGGTTGGG	GGACACCTTC	GTCCTCACCC	TGAGCGACTT
315	CCGCCGAGAG	AACGAGGGCT	ACTATTTCTG	CTCGGCCCTG	AGCAACTCCA
365	TCATGTACTT	CAGCCACTTC	GTGCCGGTCT	TCCTGCCAGC	GAAGCCCACC
415	ACGACGCCAG	CGCCGCGACC	ACTAACACCG	GCGCCCACCA	TCGCGTCGCA
465	GCCCCTGTCC	CTGCGCCCAG	AGGCGTGCCG	GCCAGCGGCG	GGGGGCGCAG
515	TGCACACGAG	GGGGCTGGAC	TTCGCCTGTG	ATATCTACAT	CTGGGCGCCC
565	CTGGCCGGGA	CTTGTGGGGT	CCTTCTCCTG	TCACTGGTTA	TCACCCTTTA
615	CTGCAACCAC	AGGAACCGAA	GACGTGTTTG	CAAATGTCCC	CGGCCTGTGG
665	TCAAATCGGG	AGACAAGCCC	AGCCTTTCGG	CGAGATACGT	CTAACCCTGT
715	GCAACAGCCA	CTACATGAAT	TCC		

FIG. 17



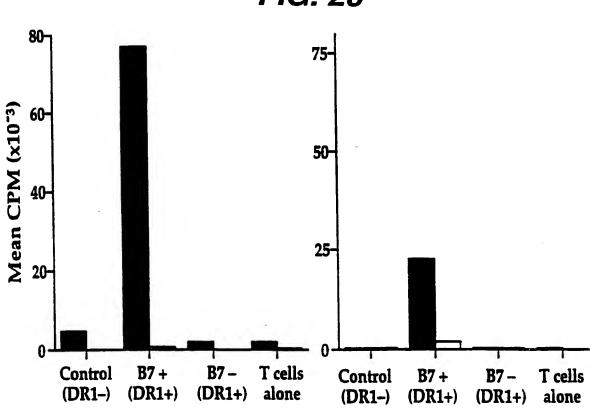


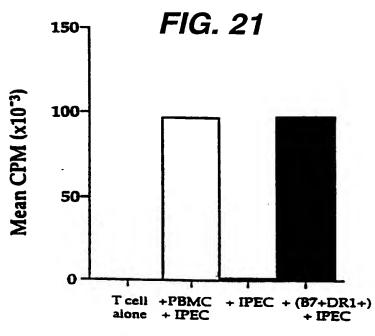


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FIG. 20





Stimulator population